* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

* * * * *

Applicants: Michelle PRUDHOMME, et al.

Serial No.: 10/672,418

Filed : September 26, 2003

Title : [3,4-a:3,4-c] carbazole compounds.

* * * * *

HON. COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

CLAIM TO PRIORITY AND FILING OF PRIORITY DOCUMENT
UNDER 37 CFR § 1.55 AND 35 USC § 119

Sir:

Herewith please find a certified copy of French priority application Serial No. 0212847 filed October 16, 202, and certified translation thereof into English, the right of priority of which was claimed upon filing of the above-identified application, and which claim is hereby repeated.

Respectfully submitted,
THE FIRM OF HUESCHEN & SAGE

By: G. PATRICK SAGE

G. PATRICK SAGE, ATTORNEY

Dated: March 11, 2004.

Customer No. 25,666
500 Columbia Plaza
350 East Michigan Ave.
Kalamazoo, MI 49007
(616) 382-0030

Enclosures: Certified copy of French priority application Serial No. 0212847,
Certified translation thereof into English, and
Return postal card receipt.

CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to Commissioner of Patents and Trademarks, Alexandria, VA 22313-1450, on this date.

HUESCHEN AND SAGE

Dated: March 11, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, VIVIEN IRENE COULSON, declare:

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 96 Langley Road, Watford, Hertfordshire, WD17 4PJ;

2. That I am well acquainted with the French and English languages;

3. That the attached is a true translation into the English language of the certified copy of French Patent Application No. 0212847 filed 16 October 2002;

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

Declared this 26th day of November 2003

V.I. Coulson

V.I. COULSON

FRENCH REPUBLIC

NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

PATENT OF INVENTION

UTILITY CERTIFICATE - CERTIFICATE OF ADDITION

OFFICIAL COPY

The Director General of the National Institute for Industrial Property certifies that the attached document is the true certified copy of an application for an Industrial Property Right filed at the Institute.

Issued in Paris, 21 July 2003

For the Director General of the
National Institute for
Industrial Property
The Head of the Patents Division

(signature)

Martine PLANCHE

NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

HEAD OFFICE

26 bis, rue de Saint Petersbourg
75800 PARIS cedex 08
Tel.: 33 (0)1 53 04 53 04 Fax: 33 (0)1 53 04 45 23 www.inpi.fr

National Public Institution created by law
no. 51-444 of 19 April 1951

1st filing

INPI NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

PATENT OF INVENTION UTILITY CERTIFICATE

Intellectual Property Code - Book VI

26 bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Tel.: 01 53 04 53 04 Fax: 01 42 94 86 54

REQUEST FOR GRANT 1/2

Reserved for INPI

This form is to be completed legibly in black ink

DEPOSITION OF DOCUMENTS **DATE** 16OCT. 2002 **PLACE** 75 INPI PARIS **NATIONAL REGISTRATION NO. ATTRIBUTED BY THE INPI** 0212847 **FILING DATE ATTRIBUTED BY THE INPI** 16 OCT. 2002	**1 NAME AND ADDRESS OF THE APPLICANT OR OF THE AUTHORISED AGENT TO WHOM CORRESPONDENCE MUST BE ADDRESSED** LES LABORATOIRES SERVIER Direction Brevets 12, place de La Défense 92415 COURBEVOIE Cedex
Your references for this file *(optional)* 29285	
Confirmation of a deposit by facsimile	☐ No. attributed by the INPI to the facsimile

2 NATURE OF THE APPLICATION	**Mark one of the following 4 boxes**
Patent Application	☒
Application for a Utility Certificate	☐
Divisional Application	☐
Initial patent application	No. Date
or initial utility certificate application	No. Date
Conversion of a European Patent Application	☐
Initial patent application	No. Date

3 TITLE OF THE INVENTION (maximum 200 characters or spaces)

New [3,4-a:3,4-c]carbazole compounds, a process for their preparation and pharmaceutical compositions containing them

4 DECLARATION OF PRIORITY OR REQUEST FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION	Country or organisation Date No. Country or organisation Date No. Country or organisation Date No. ☐ **If there are other priorities, mark the box and use the "Continuation" form**
5 APPLICANT	☐ **If there are other Applicants, mark the box and use the "Continuation" form**
Name or company name	LES LABORATOIRES SERVIER
Forenames	
Legal nature	
SIREN No.	
APE-NAF Code	
Address — Street	12, place de La Défense
Address — Postal code and town	92415 COURBEVOIE Cedex
Country	FRANCE
Nationality	FRENCH
Telephone no. *(optional)*	01.55.72.60.00
Fax no. *(optional)*	01.55.72.72.13
E-mail address *(optional)*	

1st filing

INPI NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

PATENT OF INVENTION UTILITY CERTIFICATE

REQUEST FOR GRANT 2/2

Reserved for INPI

DEPOSITION OF DOCUMENTS **DATE** 16 OCT 2002 **PLACE** 75 INPI PARIS **NATIONAL REGISTRATION NO. ATTRIBUTED BY THE INPI** 0212847	
Your references for this file: *(optional)*	29285
6 AUTHORISED AGENT	
Name	WENGER
Forename	Sabine
Practice or company	LES LABORATOIRES SERVIER
No. of standing power of attorney and/or of contractual bond	
Address — Street	12, place de La Défense
Address — Postal code and town	92415 COURBEVOIE Cedex
Telephone no. *(optional)*	01.55.72.60.00
Fax no. *(optional)*	01.55.72.72.13
E-mail address *(optional)*	
7 INVENTOR(S)	
The inventors are the Applicants	☐ Yes ☒ No **In this case, supply a separate declaration of inventorship**
8 SEARCH REPORT	**For a patent application only (including division and conversion)**
immediate drawing up	☒
or deferred drawing up	☐
Payment of the fees in instalments	**Payment in three instalments, for natural persons only** ☐ Yes ☐ No
9 REDUCTION IN FEES	**For natural persons only** ☐ Requested for the first time for this invention *(attach a notice of non-imposition)* ☐ Requested prior to this deposit *(attach a copy of the admissibility decision for this invention or indicate its reference)*
If you have used the "Continuation" form, indicate the number of pages attached	
10 SIGNATURE OF THE APPLICANT OR OF THE AUTHORISED AGENT **(Name and position of signatory)** (signature) **Sabine WENGER,** Patent Engineer	**STAMP OF THE PREFECTURE OR OF THE INPI** (signature)

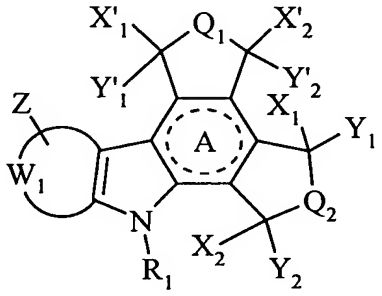
Law No. 78-17 of 6 January 1978 relating to information processing, data files and rights applies to the responses made on this form. It guarantees right of access to and correction of the data concerning you at the INPI.

The present invention relates to new [3,4-a:3,4-c]carbazole compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The needs of anti-cancer therapy call for the constant development of new anti-proliferative agents, with the aim of obtaining medicaments that are both more active and better tolerated. The compounds of the present invention exhibit in particular anti-tumour properties, which accordingly render them useful in the treatment of cancers.

The Patent Applications WO 95/07910 and WO 96/04906 describe indole compounds and claim them, on the one hand, for their antiviral activity and, on the other hand, for the treatment and prevention of restenosis. The Patent Applications WO 00/47583, WO 97/21677 and WO 96/11933 disclose cyclopenta[g]pyrrolo[3,4-*e*]indole compounds which are fused on the indole moiety and the cyclopentene moiety of the compounds to an aromatic or non-aromatic ring system and which optionally contain hetero atoms. Those compounds exhibit pharmacological activities that render them useful in the treatment of cancer. Patent Application WO 01/85686 describes pyrrolo[3,4-c]carbazole compounds for use in the treatment of neurodegenerative diseases, inflammation, ischaemia and cancer. Patent Application WO 02/24699 describes tetrahydrocarbazole compounds for use on the one hand in antimicrobial treatment and on the other hand as a deodorant and disinfectant of the skin.

The present invention relates more especially to compounds of formula (I) :



(I)

wherein :

- **A** represents a saturated or partially or fully unsaturated ring, wherein the unsaturation optionally confers an aromatic character on the ring,

- W_1, together with the carbon atoms to which it is bonded, represents a phenyl group or a pyridyl group,

- **Z** represents a group of formula U–V wherein :
  - ✓ U represents a single bond or a linear or branched (C_1-C_6)alkylene chain optionally substituted by one or more identical or different groups selected from halogen and hydroxy, and/or optionally containing one or more unsaturated bonds,
  - ✓ V represents a group selected from a hydrogen atom, a halogen atom and the groups cyano, nitro, azido, linear or branched (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, hydroxy, linear or branched (C_1-C_6)alkoxy, aryloxy, aryl-(C_1-C_6)alkoxy in which the alkoxy moiety may be linear or branched, formyl, carboxy, aminocarbonyl, NR_3R_4, $-C(O)-T_1$, $-C(O)-NR_3-T_1$, $-NR_3-C(O)-T_1$, $-O-C(O)-T_1$, $-C(O)-O-T_1$, $-O-T_2-NR_3R_4$, $-O-T_2-OR_3$, $-O-T_2-CO_2R_3$, $-NR_3-T_2-NR_3R_4$, $-NR_3-T_2-OR_3$, $-NR_3-T_2-CO_2R_3$ and $-S(O)_t-R_3$,

  wherein :

  - ⇨ R_3 and R_4, which may be indentical or different, each represents a group selected from a hydrogen atom and the groups linear or branched (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, or
    R_3+R_4, with the nitrogen atom carrying them, together form a saturated monocyclic or bicyclic heterocycle that has from 5 to 10 atoms, optionally contains in the ring system a second hetero atom selected from oxygen and nitrogen, and is optionally substituted by a group selected from linear or branched (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, hydroxy, linear or branched (C_1-C_6)alkoxy, amino, linear or branched mono-(C_1-C_6)alkylamino, and di(C_1-C_6)alkylamino in which the alkyl moieties may be linear or branched,
  - ⇨ T_1 represents a group selected from linear or branched (C_1-C_6)alkyl that is optionally substituted by a group selected from $-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$ and $-C(O)NR_3R_4$ wherein R_3 and R_4 are as defined hereinbefore; aryl, and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched; or a linear or branched (C_2-C_6)alkenyl chain optionally substituted by a group selected from

$-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$ and $-C(O)NR_3R_4$ wherein R_3 and R_4 are as defined hereinbefore,

⇨ T_2 represents a linear or branched (C_1-C_6)alkylene chain,

⇨ t represents an integer of from 0 to 2 inclusive,

- **Q_1** represents a group selected from an oxygen atom and an NR_2 group, wherein R_2 represents a group selected from a hydrogen atom and the groups linear or branched (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, cycloalkyl, cycloalkyl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, $-OR_3$, $-NR_3R_4$, $-O-T_2-NR_3R_4$, $-NR_3-T_2-NR_3R_4$, linear or branched (C_1-C_6)hydroxyalkylamino, di((C_1-C_6)hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, $-C(O)-R_3$ and $-NH-C(O)-R_3$; or a linear or branched (C_1-C_6)alkylene chain optionally substituted by one or more identical or different groups selected from halogen atoms and the groups cyano, nitro, $-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$, linear or branched (C_1-C_6)hydroxyalkylamino, di((C_1-C_6)hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, and $-C(O)-NHR_3$, the groups R_3, R_4 and T_2 being as defined hereinbefore,

- **Q_2** represents a group selected from an oxygen atom and an NR'_2 group wherein R'_2 represents a group selected from a hydrogen atom and the groups linear or branched (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, cycloalkyl, cycloalkyl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, $-OR_3$, $-NR_3R_4$, $-O-T_2-NR_3R_4$, $-NR_3-T_2-NR_3R_4$, linear or branched (C_1-C_6)hydroxyalkylamino, di((C_1-C_6)hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, $-C(O)-R_3$ and $-NH-C(O)-R_3$; or a linear or branched (C_1-C_6)alkylene chain optionally substituted by one or more identical or different groups selected from halogen atoms and the groups cyano, nitro, $-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$, linear or branched (C_1-C_6)hydroxyalkylamino, di((C_1-C_6)-hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, and $-C(O)-NHR_3$, the groups R_3, R_4 and T_2 being as defined hereinbefore,

- **X_1** represents a group selected from a hydrogen atom and the groups hydroxy, linear or

branched (C_1-C_6)alkoxy, mercapto, and linear or branched (C_1-C_6)alkylthio,

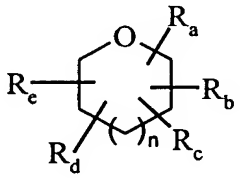
- Y_1 represents a hydrogen atom, or
- X_1 and Y_1, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

- X_2 represents a group selected from a hydrogen atom and the groups hydroxy, linear or branched (C_1-C_6)alkoxy, mercapto and linear or branched (C_1-C_6)alkylthio,
- Y_2 represents a hydrogen atom, or
- X_2 and Y_2, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

- X'_1 represents a group selected from a hydrogen atom and the groups hydroxy, linear or branched (C_1-C_6)alkoxy, mercapto and linear or branched (C_1-C_6)alkylthio,
- Y'_1 represents a hydrogen atom, or
- X'_1 and Y'_1, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

- X'_2 represents a group selected from a hydrogen atom and the groups hydroxy, linear or branched (C_1-C_6)alkoxy, mercapto and linear or branched (C_1-C_6)alkylthio,
- Y'_2 represents a hydrogen atom, or
- X'_2 and Y'_2, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

- R_1 represents a group selected from a hydrogen atom, a linear or branched (C_1-C_6)alkyl group that is optionally substituted by one or more groups hydroxy, linear or branched (C_1-C_6)alkoxy, linear or branched (C_1-C_6)hydroxyalkoxy, or a group of formula (a) :



(a)

wherein :

- ✓ R_a, R_b, R_c and R_d, which may be identical or different, each represents,

independently of the others, a bond or a group selected from a hydrogen atom, a halogen atom, and the groups hydroxy, linear or branched (C_1-C_6)alkoxy, aryloxy, aryl-(C_1-C_6)alkoxy in which the alkoxy moiety may be linear or branched, linear or branched (C_1-C_6)alkyl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, aryl, $-NR_3R_4$ wherein R_3 and R_4 are as defined hereinbefore, azido, $-N=NR_3$ (wherein R_3 is as defined hereinbefore), and $-O-C(O)-R_5$ wherein R_5 represents a linear or branched (C_1-C_6)alkyl group (optionally substituted by one or more groups selected from halogen, hydroxy, amino, linear or branched (C_1-C_6)-alkylamino, and di(C_1-C_6)alkylamino in which the alkyl moieties may be linear or branched), aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, cycloalkyl or heterocycloalkyl,

- ✓ **R_e** represents a methylene group ($H_2C=$) or a group of formula $-U_1-R_a$ wherein U_1 represents a single bond or a methylene group and R_a is as defined hereinbefore,
- ✓ **n** is 0 or 1,

it being understood that the group of formula (a) is bonded to the nitrogen atom by R_a, R_b, R_c, R_d or R_e,

to their enantiomers, diastereoisomers, and also to addition salts thereof with a pharmaceutically acceptable acid or base,

with the proviso that the compounds of formula (I) are other than the following compounds:

- 3b,6a,6b,7-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;
- 5-ethyl-3b,6a,6b,7-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;
- 3b,6a,7,11c-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;
- 3b,6a,6b,7-tetrahydrofuro[3,4-a]pyrrolo[3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;

wherein aryl is understood to mean a phenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl or indanyl group, each of those groups optionally being

substituted by one or more identical or different groups selected from halogen, linear or branched (C_1-C_6)alkyl, linear or branched (C_1-C_6)trihaloalkyl, hydroxy, linear or branched (C_1-C_6)alkoxy, and amino optionally substituted by one or two linear or branched (C_1-C_6)alkyl groups.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid, etc...

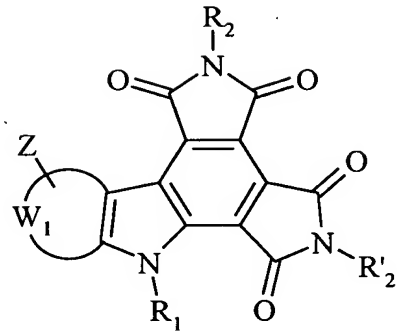
Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc...

Preferred compounds of the invention are those wherein X_1 and Y_1, with the carbon atom carrying them, together form a carbonyl group, X_2 and Y_2, with the carbon atom carrying them, together form a carbonyl group, X'_1 and Y'_1, with the carbon atom carrying them, together form a carbonyl group and X'_2 and Y'_2, with the carbon atom carrying them, together form a carbonyl group.

Advantageously, the Q_1 group preferred according to the invention is the group $-NR_2$ wherein R_2 is as defined for formula (I).

Advantageously, the Q_2 group preferred according to the invention is the group $-NR'_2$ wherein R'_2 is as defined for formula (I).

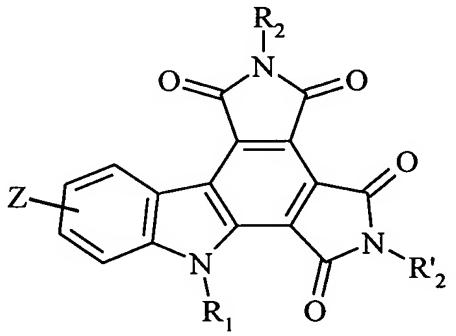
According to an advantageous embodiment, preferred compounds of the invention are compounds of formula (I) corresponding more especially to formula (IA) :



(IA)

wherein R_1, R_2, R'_2, W_1 and Z are as defined for formula (I).

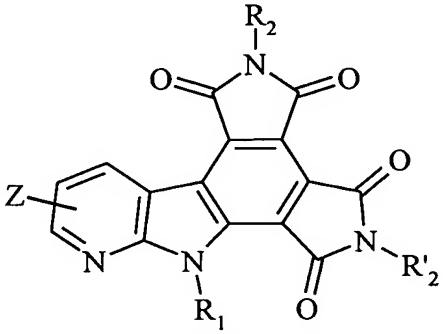
According to a second advantageous embodiment, preferred compounds of the invention are compounds of formula (I) corresponding more especially to formula (IB) :



(IB)

wherein R_1, R_2, R'_2 and Z are as defined for formula (I).

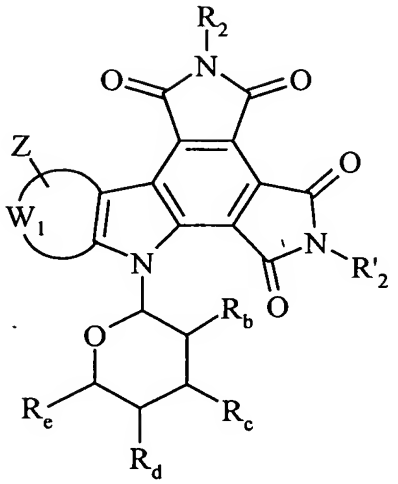
According to a third advantageous embodiment, preferred compounds of the invention are compounds of formula (I) corresponding more especially to formula (IC) :



(IC)

wherein R_1, R_2, R'_2 and Z are as defined for formula (I).

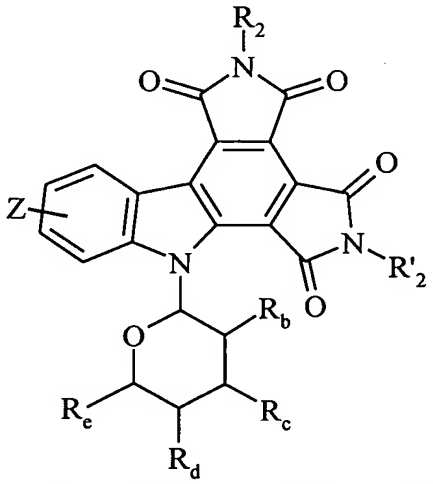
According to a fourth advantageous embodiment, preferred compounds of the invention are compounds of formula (I) corresponding more especially to formula (ID) :



(ID)

wherein R_2, R'_2, W_1, Z, R_b, R_c, R_d and R_e are as defined for formula (I).

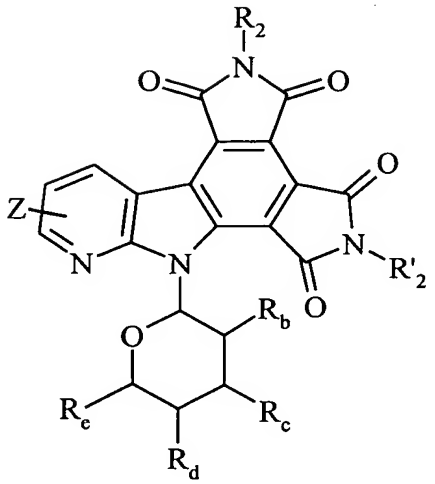
According to a fifth advantageous embodiment, preferred compounds of the invention are compounds of formula (I) corresponding more especially to formula (IE) :



(IE)

wherein R_2, R'_2, Z, R_b, R_c, R_d and R_e are as defined for formula (I).

According to a sixth advantageous embodiment, preferred compounds of the invention are compounds of formula (I) corresponding more especially to formula (IF) :



(IF)

wherein R_2, R'_2, Z, R_b, R_c, R_d and R_e are as defined for formula (I).

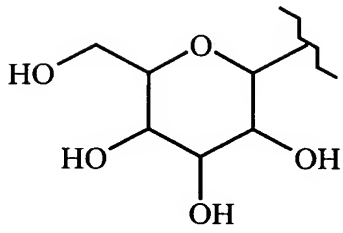
Preferably, the substituent Z preferred according to the invention is the hydrogen atom.

In an embodiment of interest, the group R_1 preferred according to the invention is the hydrogen atom.

In an embodiment of interest, the groups R_2 preferred according to the invention are the hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, and a linear or branched $(C_1\text{-}C_6)$alkylene chain substituted by an NR_3R_4 group wherein R_3 and R_4 are as defined for formula I.

In an embodiment of interest, the groups R'_2 preferred according to the invention are the hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, and a linear or branched $(C_1\text{-}C_6)$alkylene chain substituted by an NR_3R_4 group wherein R_3 and R_4 are as defined for formula (I).

In an embodiment of interest, the group of formula (a) preferred according to the invention is the glucopyranosyl group of formula:

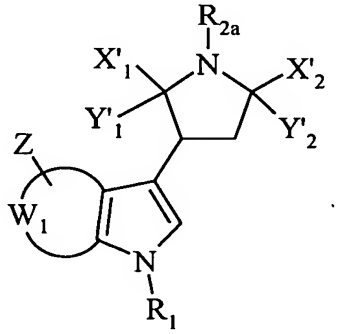


The following are preferred compounds according to the invention:

- 1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone,
- 2-methyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone,
- 2,5-dimethyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone,
- 2-[2-(diethylamino)ethyl]-5-methyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6-(2*H*,5*H*,7*H*)-tetrone.

The enantiomers, diastereoisomers, and addition salts with a pharmaceutically acceptable acid or base, of the preferred compounds form an integral part of the invention.

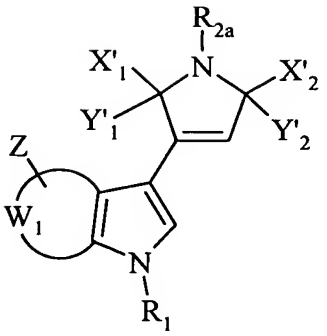
The present invention relates also to a process for the preparation of compounds of formula (I), which is characterised in that there is used as starting material a compound of formula (II) :



(II)

wherein R_{2a} represents a hydrogen atom or a methyl group and R_1, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined for formula (I),

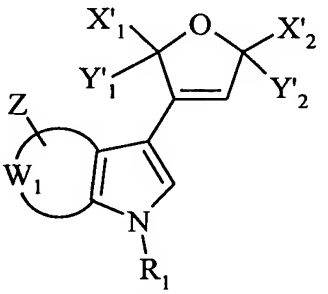
which is treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to yield a compound of formula (III) :



(III)

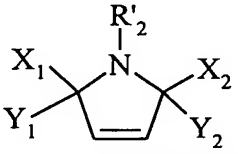
wherein R_1, R_{2a}, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,
which compound of formula (III) is :

* *either* treated with aqueous sodium hydroxide solution and then placed in the presence of hydrochloric acid to yield a compound of formula (IV) :



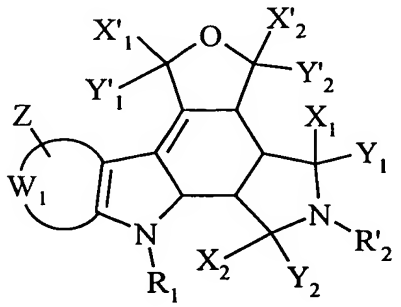
(IV)

wherein R_1, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,
which compound of formula (IV) is treated with a compound of formula (V) :

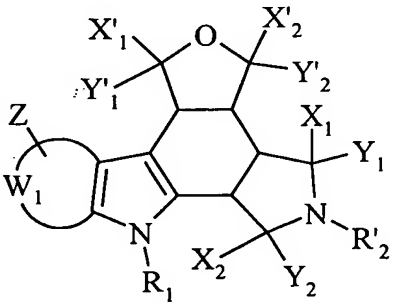


(V)

wherein R'_2, X_1, Y_1, X_2 and Y_2 are as defined for formula (I) to yield a compound of formula (I/a) and (I/b), a particular case of the compounds of formula (I) :



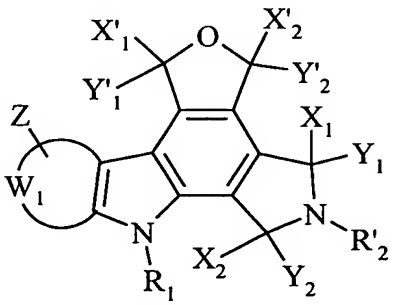
(I/a)



(I/b)

wherein R_1, R'_2, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

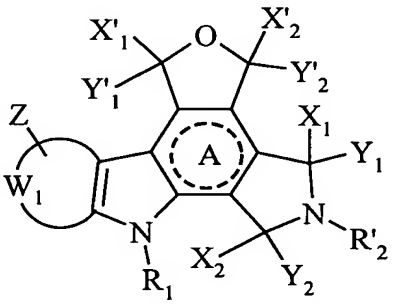
which compound(s) of formula (I/a) and/or (I/b) is(are) optionally subjected to the action of trifluoroacetic acid to yield a compound of formula (I/c), a particular case of the compounds of formula (I) :



(I/c)

wherein R_1, R'_2, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

the totality of the compounds of formulae (I/a), (I/b) and (I/c) constituting the compounds of formula (I/d) :



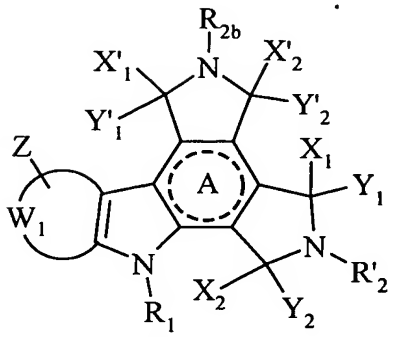
(I/d)

wherein A, R_1, R'_2, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

which compound of formula (I/d) is subjected to the action of a compound of formula (VII) :

$$R_{2b} - NH_2 \qquad (VII)$$

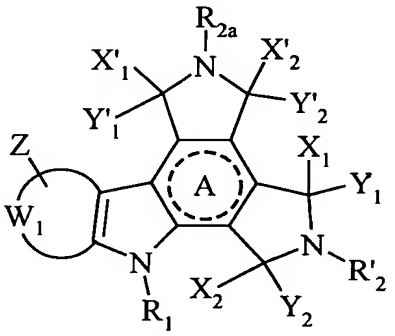
wherein R_{2b} has the same definition as R_2 in formula (I), with the exception of a hydrogen atom and a methyl group, to yield compounds of formula (I/e), a particular case of the compounds of formula (I) :



(I/e)

wherein A, R_1, R'_2, R_{2b}, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

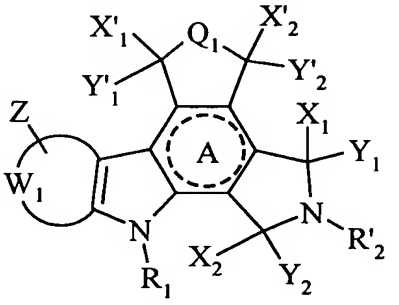
* *or* subjected in succession to the same reaction conditions as the compounds of formulae (IV), (I/a) and (I/b) to yield a compound of formula (I/f), a particular case of the compounds of formula (I) :



(I/f)

wherein A, R_1, R'_2, R_{2a}, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

the totality of the compounds (I/d), (I/e) and (I/f) constituting the compounds of formula (I/g) :

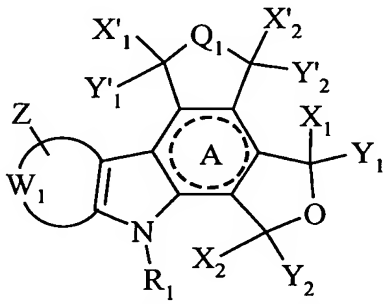


(I/g)

wherein A, R_1, R'_2, Q_1, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined

hereinbefore,

which compound of formula (I/g), when R'_2 represents a hydrogen atom or a methyl group, is optionally subjected in succession to the same reaction conditions as the compounds of formulae (III) to yield a compound of formula (I/i), a particular case of the compounds of formula (I) :

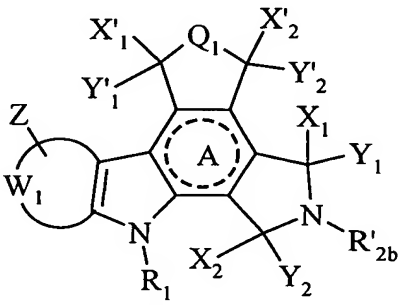


(I/i)

wherein A, R_1, Q_1, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore, which compound of formula (I/i) is optionally subjected to the action of a compound (VIII) :

$$R'_{2b} - NH_2 \quad \text{(VIII)}$$

wherein R'_{2b} has the same definition as R'_2 in formula (I), with the exception of the definitions hydrogen atom and methyl group, to yield compounds of formula (I/j), a particular case of the compounds of formula (I) :



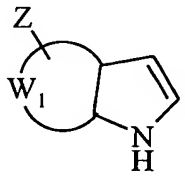
(I/j)

wherein A, R_1, R'_{2b}, Q_1, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

the compounds of formulae (I/a) to (I/j) constituting the totality of the compounds of formula (I), which, if appropriate, are purified according to conventional purification techniques, may, if desired, be separated into their different isomers according to a conventional separation technique, the substituents R_a, R_b, R_c, R_d and R_e of which may be

modified according to conventional methods of organic synthesis used in the field of sugar chemistry, and which compounds, if desired, are converted into addition salts with a pharmaceutically acceptable acid or base.

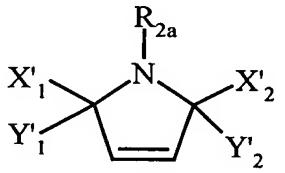
The compounds of formula (II) may advantageously be obtained starting from a compound of formula (A) :



(A)

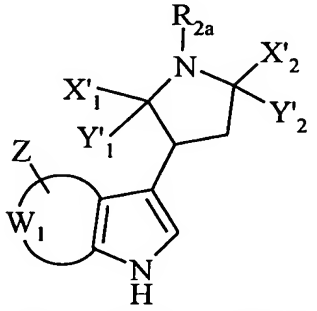
wherein W_1 and Z are as defined for formula (I), which is reacted :

* *either* with a compound of formula (B) :



(B)

wherein R_{2a}, X'_1, Y'_1, X'_2 and Y'_2 are as defined hereinbefore,
to yield a compound of formula (C) :

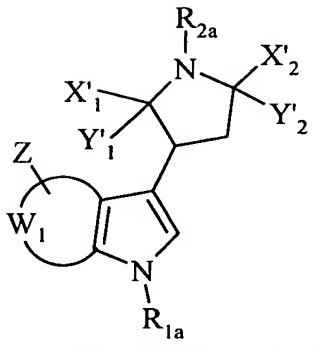


(C)

wherein R_{2a}, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,
which compound of formula (C) is optionally subjected to the action of a compound of formula (IX) :

$$R_{1a} - G \quad (IX)$$

wherein G represents a hydroxy group or a leaving group and R_{1a}, which is other than a hydrogen atom, has the same definition as R_1 in formula (I),
to yield a compound of formula (D) :

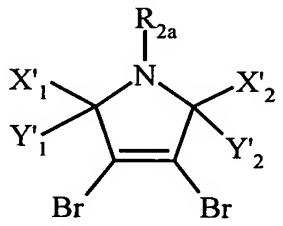


(D)

wherein R_{1a}, R_{2a}, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

the compounds of formulae (C) and (D) constituting the totality of the compounds of formula (II),

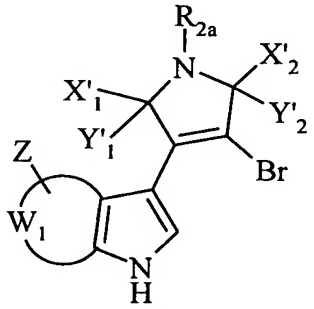
* *or* with a compound of formula (E) :



(E)

wherein R_{2a}, X'_1, Y'_1, X'_2 and Y'_2 are as defined hereinbefore, in the presence of alkylmagnesium halide,

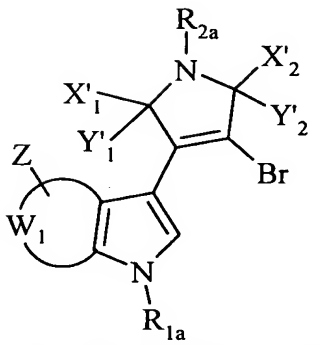
to yield a compound of formula (F) :



(F)

wherein R_{1a}, R_{2a}, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

which compound of formula (F) is optionally subjected to the same reaction conditions as the compound of formula (C), to yield a compound of formula (G) :



(G)

wherein R_{1a}, R_{2a}, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,
which compound of formula (G) is hydrogenated according to conventional methods of organic synthesis to yield a compound of formula (II).

The compounds of formulae (V), (VII), (VIII), (IX), (A), (B) and (E) are either commercially available products or are products obtained according to conventional methods of organic synthesis well known to the person skilled in the art.

The compounds of formula (I) exhibit anti-tumour properties that are of particular interest. The characteristic properties of those compounds allow them to be used therapeutically as anti-tumour agents.

The present invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), optical isomers thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base, on its own or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those which are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory administration, and especially tablets or dragées, sublingual tablets, gelatin capsules, capsules, suppositories, creams, ointments, dermal gels, injectable or drinkable preparations, aerosols, eye drops and nose drops etc...

By virtue of the pharmacological properties characteristic of the compounds of formula (I), the pharmaceutical compositions comprising the said compounds of formula (I) as active

ingredient are accordingly especially useful in the treatment of cancers.

The useful dosage varies according to the age and weight of the patient, the administration route, the nature and the severity of the disorder, and the administration of any associated treatments, and ranges from 1 mg to 500 mg per day in one or more administrations.

The Examples that follow illustrate the invention but do not limit in in any way. The starting materials employed are known products or products prepared according to known procedures.

The structures of the compounds described in the Examples were determined according to customary spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...).

PREPARATION A :

3b,6a,6b,7-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone

Step A : 3-(1*H*-indol-3-yl)-2,5-pyrrolidinedione

The expected product is obtained in accordance with the process described by J. Bergman *et al.* (Tetrahedron, 1999, 55, pp. 2363-2370).

Step B : 3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione

The expected product is obtained in accordance with the process described by J. Bergman *et al.* (Tetrahedron, 1999, 55, pp. 2363-2370).

Step C : 3b,6a,6b,7-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6-(2*H*,3a*H*,5*H*)-tetrone

The expected product is obtained in accordance with the process described by J. Bergman *et al.* (J. Chem. Soc., Perkin Trans. I, 2000. pp. 2615-2621).

PREPARATION B :

3-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione

Step A : 3-(1*H*-indol-3-yl)-1-methyl-2,5-pyrrolidinedione

The expected product is obtained in accordance with the process described by J. Bergman *et al.* (Tetrahedron, 1999, 55, pp. 2363-2370).

Step B : 3-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione

The expected product is obtained in accordance with the process described by J. Bergman *et al.* (Tetrahedron, 1999, 55, pp. 2363-2370).

PREPARATION C :

3-[5-(benzyloxy)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrole-2,5-dione

Step A : 3-[5-(benzyloxy)-1*H*-indol-3-yl]-1-methyl-2,5-pyrrolidinedione

A mixture of 5-benzyloxy-indole (8 mmol) and N-methylmaleimide (8 mmol) in 8 ml of acetic acid is refluxed for 48 hours. The acetic acid is evaporated off. Purification by chromatography on silica gel (ethyl acetate/cyclohexane : 2/8 to 7/3) allows the expected product to be obtained.

Melting point : 49-53°C

IR (KBr) : $\nu_{C=O}$ = 1690, 1700 cm^{-1} ; ν_{NH} = 3300-3500 cm^{-1}

Mass spectrum (FAB) : 335.14 [$M+H^+$]

Step B : 3-[5-(benzyloxy)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrole-2,5-dione

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2 mmol) in 20 ml of dioxane is slowly added to a solution of the compound obtained in the above Step (2 mmol) in 20 ml

of dioxane. The reaction mixture is stirred overnight at ambient temperature. After filtration, followed by removal of the dioxane by evaporation, the reaction mixture is taken up in isopropanol for recrystallisation. The expected product is obtained by filtration and washing with isopropanol the precipitate that has formed.

Melting point : 176-182°C

IR (KBr) : $\nu_{C=O}$ = 1690, 1700 cm^{-1} ; ν_{NH} = 3300-3440 cm^{-1}

Mass spectrum (FAB) : 333.12 [$M+H^+$]

PREPARATION D :

3-(1*H*-indol-3-yl)-2,5-furandione

A mixture of the compound of Preparation B (0.884 mmol) and sodium hydroxide pellets (12.5 mmol) in 100 ml of distilled water is refluxed for 2 hours. After cooling the reaction mixture, concentrated hydrochloric acid is added dropwise until a precipitate is formed. The expected product is isolated by filtration of the precipitate.

Melting point : 210-214°C

IR (KBr) : $\nu_{C=O}$ = 1740, 1800 cm^{-1} ; ν_{NH} = 3320 cm^{-1}

PREPARATION E :

3-(1*H*-pyrrolo[2,3-b]pyrid-3-yl)-1*H*-pyrrole-2,5-dione

Step A : 3-bromo-4-(1*H*-pyrrolo[2,3-b]pyrid-3-yl)-1*H*-pyrrole-2,5-dione

A solution of ethylmagnesium bromide is prepared from magnesium (12.7 mmol) suspended in bromoethane (12.7 mmol) and dry tetrahydrofuran (5 ml). The solution is stirred for 1 hour at ambient temperature and then 7-azaindole (12.7 mmol), dissolved in 40 ml of anhydrous toluene, is added dropwise. After 1 hour 30 minutes' stirring at ambient temperature, a solution of 2,3-dibromomaleimide (3.53 mmol) in 40 ml of anhydrous toluene is added dropwise. After 20 minutes, 60 ml of dry dichloromethane are added, and then the reaction mixture is stirred for 75 hours at 40°C and subsequently hydrolysed with

a saturated aqueous ammonium chloride solution. The organic product is extracted with ethyl acetate, and then the organic phases are combined, dried over magnesium sulphate and filtered. After removal of the solvent by evaporation, and purification of the residue by chromatography on silica gel (cyclohexane/ethyl acetate : 3/2), the expected product is isolated.

Step B : 3-(1*H*-pyrrolo[2,3-b]pyrid-3-yl)-2,5-pyrrolidinedione

A mixture of the compound obtained in the above Step (0.327 mmol) and a catalytic amount of 10% palladium-on-carbon in methanol (40 ml) is hydrogenated at one atmosphere for 24 hours. The mixture is filtered over Celite and the expected product is obtained after purification of the residue by chromatography on silica gel using ethyl acetate as eluant.

Step C : 3-(1*H*-pyrrolo[2,3-b]pyrid-3-yl)-1*H*-pyrrole-2,5-dione

The expected product is obtained in accordance with the procedure described in Step B of Preparation C, starting from the compound of the above Step.

PREPARATION F :

1-methyl-3-[1-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-1*H*-pyrrolo[2,3-b]pyrid-3-yl]-1*H*-pyrrole-2,5-dione

Step A : 3-bromo-1-methyl-4-(1*H*-pyrrolo[2,3-b]pyrid-3-yl)-1*H*-pyrrole-2,5-dione

The expected product is obtained in accordance with the procedure described in Step A of Preparation E, using N-methyl-2,3-dibromomaleimide as substrate.

Melting point : 158°C

Step B : **3-bromo-1-methyl-4-[1-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-1*H*-pyrrolo[2,3-b]pyrid-3-yl]-1*H*-pyrrole-2,5-dione**

2,3,4,6-Tetra-O-acetylglucopyranose (1.95 mmol) and triphenylphosphine (1.95 mmol) are added dropwise to a solution of the compound of the above Step (0.927 mmol) dissolved in 40 ml of dry tetrahydrofuran. The temperature is slowly brought back to ambient temperature, and then the reacton mixture is stirred for a further 15 hours. Following hydrolysis, the organic product is extracted with ethyl acetate. The organic phases are combined, dried over magnesium sulphate and filtered, and the solvent is evaporated off. The expected product is obtained after purification by chromatography on silica gel.

Step C : **1-methyl-3-[1-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-1*H*-pyrrolo[2,3-b]pyrid-3-yl]-2,5-pyrrolidinedione**

The expected product is obtained in accordance with the procedure described in Step B of Preparation E, starting from the compound of the above Step.

Step D : **1-methyl-3-[1-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-1*H*-pyrrolo[2,3-b]pyrid-3-yl]-1*H*-pyrrole-2,5-dione**

The expected product is obtained in accordance with the procedure described in Step B of Preparation C, starting from the compound of the above Step.

EXAMPLE 1 : 1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6-(2*H*,5*H*,7*H*)-tetrone

The compound of Preparation A (0.388 mmol) is heated at reflux for 24 hours in 24 ml of dioxane in the presence of trifluoroacetic acid (400 µl). After removal of the solvent by evaporation, the crystals are taken up in ethyl acetate and washed with a saturated sodium hydrogen carbonate solution and a saturated sodium chloride solution. The expected product is obtained by filtration of the crystals over a frit.

Melting point : > 300°C

IR (KBr) : $\nu_{C=O}$ = 1690, 1730, 1745, 1780 cm^{-1} ; ν_{NH} = 3280-3380 cm^{-1}
Mass spectrometry (FAB) : 306.05 $[M+H^+]$

EXAMPLE 2 : 2,5-dimethyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone

A mixture of the compound of Preparation B (1 mmol) and N-methylmaleimide (1.10 mmol) in 17 ml of para-xylene is refluxed for 24 hours. After cooling, the yellow precipitate is filtered off and then washed with para-xylene. Chromatography on a silica column (ethyl acetate/cyclohexane : 1/1 ; ethyl acetate ; ethyl acetate/methanol : 98/2) allows a mixture of isomers to be obtained which is heated at reflux for 84 hours in 25 ml of dioxane in the presence of trifluoroacetic acid. After removal of the solvent by evaporation, the crystals are taken up in acetate and washed with a saturated sodium hydrogen carbonate solution and a saturated sodium chloride solution. The expected product is obtained by filtration of the crystals over a frit.

Melting point : > 300°C
IR (KBr) : $\nu_{C=O}$ = 1695, 1720 cm^{-1} ; ν_{NH} = 3410 cm^{-1}
Mass spectrometry (FAB) : 334.08 $[M+H^+]$

EXAMPLE 3 : 2-methyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone

The expected product is obtained in accordance with the procedure described in Example 2, starting from the compound of Preparation B and maleimide.

Melting point : > 300°C
IR (KBr) : $\nu_{C=O}$ = 1710, 1720, 1760, 1780 cm^{-1} ; ν_{NH} = 3260-3395 cm^{-1}
Mass spectrometry (FAB) : 320.06 $[M+H^+]$

EXAMPLE 4 : 10-(benzyloxy)-2,5-dimethyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone

The expected product is obtained in accordance with the procedure described in Example 2, starting from the compound of Preparation C and N-methylmaleimide.

Melting point : > 300°C

IR (KBr) : $\nu_{C=O}$ = 1700, 1720, 1775 cm^{-1} ; ν_{NH} = 3480 cm^{-1}

Mass spectrometry (FAB) : 440.12 [$M+H^+$]

EXAMPLE 5 : 5-methylfuro[3,4-c]pyrrolo[3,4-a]carbazole-1,3,4,6(5*H*,7*H*)-tetrone

The expected product is obtained in accordance with the procedure described in Example 2, starting from the compound of Preparation D and N-methylmaleimide.

Melting point : 294°C (decomposition)

IR (KBr) : $\nu_{C=O}$ = 1775, 1840 cm^{-1} ; ν_{NH} = 3370 cm^{-1}

Mass spectrometry (FAB) : 321.05 [$M+H^+$]

EXAMPLE 6 : 2-[2-(diethylamino)ethyl]-5-methyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone hydrochloride

N-*N*-diethylethylenediamine (0.132 mmol) is added dropwise to a solution of the compound of Example 5 (0.088 mmol) dissolved in 5.2 ml of anhydrous tetrahydrofuran. The mixture is heated at 65°C for 4 days with the exclusion of light and then cooled and taken up in a mixture of an aqueous 1N hydrochloric acid solution (40 ml) and ethyl acetate. The organic product is extracted with ethyl acetate. The aqueous phase is taken up in ethyl acetate and the pH is adjusted to 12 by the addition of a saturated aqueous sodium hydrogen carbonate solution. The organic product is extracted with ethyl acetate. The organic phases are combined, dried over magnesium sulphate and filtered, and the solvent is evaporated off in the cold. To a solution, cooled to 0°C, of the amine so obtained dissolved in 400 µl of methanol there is added dropwise an aqueous 1N hydrochloric acid

solution (190 µl). The mixture is stirred for 30 minutes. The solvent is evaporated off, allowing the expected product to be isolated.

Melting point : 184°C (decomposition)

IR (KBr) : $\nu_{C=O}$ = 1710, 1720, 1765, 1775 cm^{-1} ; ν_{NH} = 3300-3600 cm^{-1}

Mass spectrometry (FAB) : 419.17 $[M+H^+]$

EXAMPLE 7 : 1*H*-pyrido[2,3-b]dipyrrolo[3,4-e:3,4-g]indole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone

The expected product is obtained in accordance with the procedure described in Example 2, starting from the compound of Preparation E and maleimide.

EXAMPLE 8 : 2-methyl-7-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-1*H*-pyrido[2,3-b]dipyrrolo[3,4-e:3,4-g]indole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone

The expected product is obtained in accordance with the procedure described in Example 2, starting from the compound of Preparation F and maleimide.

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE 9 ***In vitro* activity**

- ***L1210 murine leukaemia***

L1210 murine leukaemia was used *in vitro*. The cells are cultured in RPMI 1640 complete culture medium containing 10 % foetal calf serum, 2mM glutamine, 50 units/ml of penicillin, 50 µg/ml of streptomycin and 10mM Hepes, pH : 7.4. The cells are distributed on microplates and are exposed to the cytotoxic compounds for 4 doubling periods, or 48 hours. The number of viable cells is then quantified by a colorimetric assay, the Microculture Tetrazolium Assay (J. Carmichael *et al.*, Cancer Res.; 47, 936-942 (1987)). The results are expressed as the IC_{50}, the concentration of cytotoxic agent that inhibits the

proliferation of the treated cells by 50 %. All of the products of the invention exhibit good cytotoxicity in relation to this cell line.

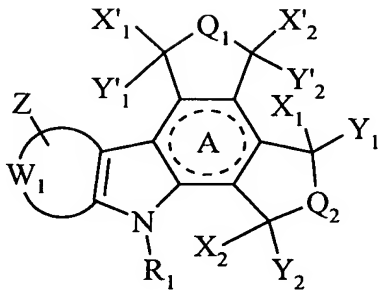
EXAMPLE 10 : Pharmaceutical composition : injectable solution

Compound of Example 1 ..... 10 mg

Distilled water for injectable preparations..... 25 ml

CLAIMS

1- Compounds of formula (I) :



(I)

wherein :

- **A** represents a saturated or partially or fully unsaturated ring, wherein the unsaturation optionally confers an aromatic character on the ring,

- **W_1**, together with the carbon atoms to which it is bonded, represents a phenyl group or a pyridyl group,

- **Z** represents a group of formula U–V wherein :
  - ✓ U represents a single bond or a linear or branched (C_1-C_6)alkylene chain optionally substituted by one or more identical or different groups selected from halogen and hydroxy, and/or optionally containing one or more unsaturated bonds,
  - ✓ V represents a group selected from a hydrogen atom, a halogen atom and the groups cyano, nitro, azido, linear or branched (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, hydroxy, linear or branched (C_1-C_6)alkoxy, aryloxy, aryl-(C_1-C_6)alkoxy in which the alkoxy moiety may be linear or branched, formyl, carboxy, aminocarbonyl, NR_3R_4, $–C(O)–T_1$, $-C(O)-NR_3-T_1$, $–NR_3–C(O)–T_1$, $-O–C(O)–T_1$, $–C(O)–O–T_1$, $–O–T_2–NR_3R_4$, $-O-T_2-OR_3$, $–O–T_2–CO_2R_3$, $-NR_3-T_2-NR_3R_4$, $–NR_3–T_2–OR_3$, $–NR_3–T_2–CO_2R_3$ and $–S(O)_t–R_3$,

  wherein :

  ⇨ R_3 and R_4, which may be indentical or different, each represents a group selected

from a hydrogen atom and the groups linear or branched (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, or

R_3+R_4, with the nitrogen atom carrying them, together form a saturated monocyclic or bicyclic heterocycle that has from 5 to 10 atoms, optionally contains in the ring system a second hetero atom selected from oxygen and nitrogen, and is optionally substituted by a group selected from linear or branched (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, hydroxy, linear or branched (C_1-C_6)alkoxy, amino, linear or branched mono-(C_1-C_6)alkylamino, and di(C_1-C_6)alkylamino in which the alkyl moieties may be linear or branched,

- ⇨ T_1 represents a group selected from linear or branched (C_1-C_6)alkyl that is optionally substituted by a group selected from $-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$ and $-C(O)NR_3R_4$ wherein R_3 and R_4 are as defined hereinbefore; aryl, and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched; or a linear or branched (C_2-C_6)alkenyl chain optionally substituted by a group selected from $-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$ and $-C(O)NR_3R_4$ wherein R_3 and R_4 are as defined hereinbefore,
- ⇨ T_2 represents a linear or branched (C_1-C_6)alkylene chain,
- ⇨ t represents an integer of from 0 to 2 inclusive,

- **Q_1** represents a group selected from an oxygen atom and an NR_2 group wherein R_2 represents a group selected from a hydrogen atom and the groups linear or branched (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, cycloalkyl, cycloalkyl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, $-OR_3$, $-NR_3R_4$, $-O-T_2-NR_3R_4$, $-NR_3-T_2-NR_3R_4$, linear or branched (C_1-C_6)hydroxyalkylamino, di((C_1-C_6)hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, $-C(O)-R_3$ and $-NH-C(O)-R_3$; or a linear or branched (C_1-C_6)alkylene chain optionally substituted by one or more identical or different groups selected from halogen atoms and the groups cyano, nitro, $-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$, linear or branched (C_1-C_6)hydroxyalkylamino, di((C_1-C_6)hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, and $-C(O)-NHR_3$, the groups R_3, R_4 and T_2 being as defined hereinbefore,

- **Q_2** represents a group selected from an oxygen atom and an NR'_2 group wherein R'_2 represents a group selected from a hydrogen atom and the groups linear or branched $(C_1\text{-}C_6)$alkyl, aryl, aryl-$(C_1\text{-}C_6)$alkyl in which the alkyl moiety may be linear or branched, cycloalkyl, cycloalkyl-$(C_1\text{-}C_6)$alkyl in which the alkyl moiety may be linear or branched, $-OR_3$, $-NR_3R_4$, $-O-T_2-NR_3R_4$, $-NR_3-T_2-NR_3R_4$, linear or branched $(C_1\text{-}C_6)$hydroxyalkylamino, di$((C_1\text{-}C_6)$hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, $-C(O)-R_3$ and $-NH-C(O)-R_3$; or a linear or branched $(C_1\text{-}C_6)$alkylene chain optionally substituted by one or more identical or different groups selected from halogen atoms and the groups cyano, nitro, $-OR_3$, $-NR_3R_4$, $-CO_2R_3$, $-C(O)R_3$, linear or branched $(C_1\text{-}C_6)$hydroxyalkylamino, di$((C_1\text{-}C_6)$-hydroxyalkyl)amino in which the alkyl moieties may be linear or branched, and $-C(O)-NHR_3$, the groups R_3, R_4 and T_2 being as defined hereinbefore,

- **X_1** represents a group selected from a hydrogen atom and the groups hydroxy, linear or branched $(C_1\text{-}C_6)$alkoxy, mercapto, and linear or branched $(C_1\text{-}C_6)$alkylthio,
- **Y_1** represents a hydrogen atom, or
- **X_1** and **Y_1**, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

- **X_2** represents a group selected from a hydrogen atom and the groups hydroxy, linear or branched $(C_1\text{-}C_6)$alkoxy, mercapto and linear or branched $(C_1\text{-}C_6)$alkylthio,
- **Y_2** represents a hydrogen atom, or
- **X_2** and **Y_2**, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

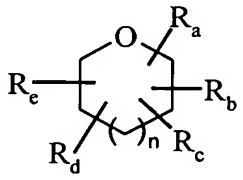
- **X'_1** represents a group selected from a hydrogen atom and the groups hydroxy, linear or branched $(C_1\text{-}C_6)$alkoxy, mercapto and linear or branched $(C_1\text{-}C_6)$alkylthio,
- **Y'_1** represents a hydrogen atom, or
- **X'_1** and **Y'_1**, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

- **X'_2** represents a group selected from a hydrogen atom and the groups hydroxy, linear or

branched (C_1-C_6)alkoxy, mercapto and linear or branched (C_1-C_6)alkylthio,

- $\mathbf{Y'_2}$ represents a hydrogen atom, or
- $\mathbf{X'_2}$ and $\mathbf{Y'_2}$, with the carbon atom carrying them, together form a carbonyl or thiocarbonyl group,

- $\mathbf{R_1}$ represents a group selected from a hydrogen atom, a linear or branched (C_1-C_6)alkyl group that is optionally substituted by one or more groups hydroxy, linear or branched (C_1-C_6)alkoxy, linear or branched (C_1-C_6)hydroxyalkoxy, or a group of formula (a) :



(a)

wherein :

- ✓ $\mathbf{R_a}$, $\mathbf{R_b}$, $\mathbf{R_c}$ and $\mathbf{R_d}$, which may be identical or different, each represents, independently of the others, a bond or a group selected from a hydrogen atom, a halogen atom, and the groups hydroxy, linear or branched (C_1-C_6)alkoxy, aryloxy, aryl-(C_1-C_6)alkoxy in which the alkoxy moiety may be linear or branched, linear or branched (C_1-C_6)alkyl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, aryl, $-NR_3R_4$ wherein R_3 and R_4 are as defined hereinbefore, azido, $-N=NR_3$ (wherein R_3 is as defined hereinbefore), and $-O-C(O)-R_5$ wherein R_5 represents a linear or branched (C_1-C_6)alkyl group (optionally substituted by one or more groups selected from halogen, hydroxy, amino, linear or branched (C_1-C_6)-alkylamino, and di(C_1-C_6)alkylamino in which the alkyl moieties may be linear or branched), aryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, cycloalkyl or heterocycloalkyl,
- ✓ $\mathbf{R_e}$ represents a methylene group ($H_2C=$) or a group of formula $-U_1-R_a$ wherein U_1 represents a single bond or a methylene group and R_a is as defined hereinbefore,
- ✓ **n** is 0 or 1,

it being understood that the group of formula (a) is bonded to the nitrogen atom by R_a, R_b, R_c, R_d or R_e,

their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically

acceptable acid or base,

with the proviso that the compounds of formula (I) are other than the following compounds:

- 3b,6a,6b,7-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;
- 5-ethyl-3b,6a,6b,7-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;
- 3b,6a,7,11c-tetrahydro-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;
- 3b,6a,6b,7-tetrahydrofuro[3,4-a]pyrrolo[3,4-c]carbazole-1,3,4,6(2*H*,3a*H*,5*H*)-tetrone ;

wherein aryl is understood to mean a phenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl or indanyl group, each of those groups optionally being substituted by one or more identical or different groups selected from halogen, linear or branched (C_1-C_6)alkyl, linear or branched (C_1-C_6)trihaloalkyl, hydroxy, linear or branched (C_1-C_6)alkoxy, and amino optionally substituted by one or two linear or branched (C_1-C_6)alkyl groups.

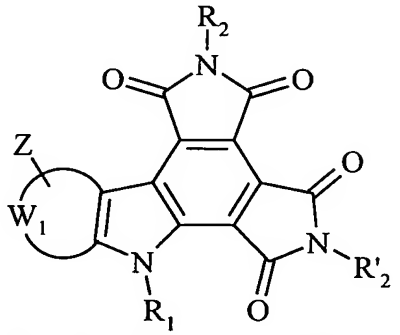
2- Compounds of formula (I) according to claim 1, characterised in that X_1 and Y_1, with the carbon atom carrying them, together form a carbonyl group, X_2 and Y_2, with the carbon atom carrying them, together form a carbonyl group, X'_1 and Y'_1, with the carbon atom carrying them, together form a carbonyl group and X'_2 and Y'_2, with the carbon atom carrying them, together form a carbonyl group, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

3- Compounds of formula (I) according to claim 1 or claim 2, characterised in that Q_1 represents an $-NR_2$ group wherein R_2 is as defined for formula (I), their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

4- Compounds of formula (I) according to any one of claims 1 to 3, characterised in that Q_2 represents an $-NR'_2$ group wherein R'_2 is as defined for formula (I), their enantiomers,

diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

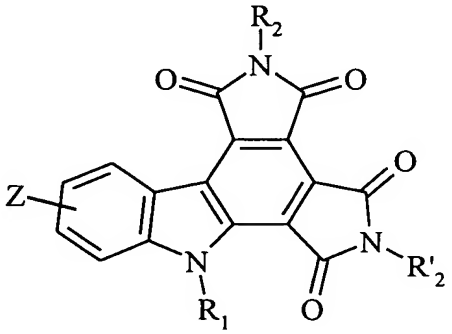
5- Compounds of formula (I) according to any one of claims 1 to 4, characterised in that they represent compounds of formula (IA) :



(IA)

wherein R_1, R_2, R'_2, W_1 and Z are as defined for formula (I), their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

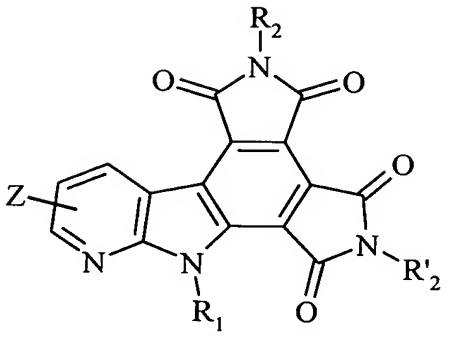
6- Compounds of formula (I) according to any one of claims 1 to 5, characterised in that they represent compounds of formula (IB) :



(IB)

wherein R_1, R_2, R'_2 and Z are as defined for formula (I), their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

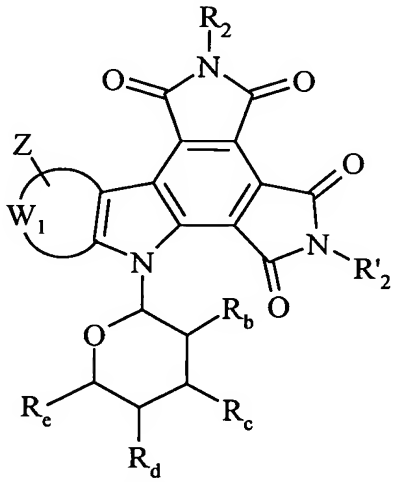
7- Compounds of formula (I) according to any one of claims 1 to 5, characterised in that they represent compounds of formula (IC) :



(IC)

wherein R_1, R_2, R'_2 and Z are as defined for formula (I), their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

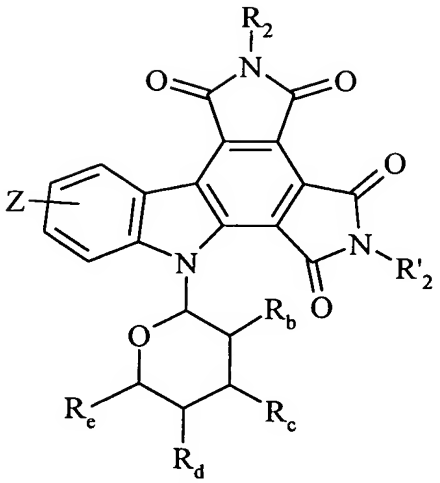
8- Compounds of formula (I) according to any one of claims 1 to 4, characterised in that they represent compounds of formula (ID) :



(ID)

wherein R_2, R'_2, W_1, Z, R_b, R_c, R_d and R_e are as defined for formula (I), their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

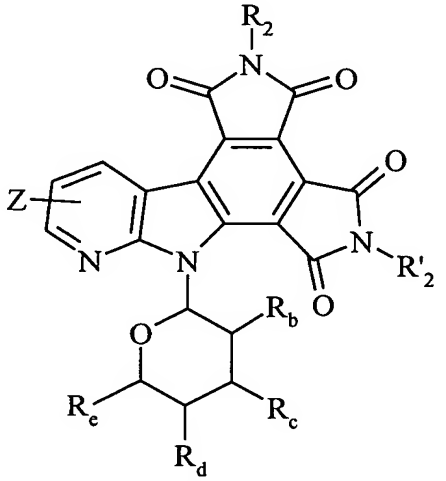
9- Compounds of formula (I) according to any one of claims 1 to 4 and 8, characterised in that they represent compounds of formula (IE) :



(IE)

wherein R_2, R'_2, Z, R_b, R_c, R_d and R_e are as defined for formula (I), their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

10- Compounds of formula (I) according to any one of claims 1 to 4 and 8, characterised in that they represent compounds of formula (IF) :



(IF)

wherein R_2, R'_2, Z, R_b, R_c, R_d and R_e are as defined for formula (I), their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

11 Compounds of formula (I) according to any one of claims 1 to 10, characterised in that Z represents a hydrogen atom, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

12- Compounds of formula (I) according to any one of claims 1 to 11, characterised in that R_1 represents a hydrogen atom, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

13- Compounds of formula (I) according to any one of claims 1 to 12, characterised in that R_2 represents a hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, or a linear or branched $(C_1\text{-}C_6)$alkylene chain substituted by an NR_3R_4 group wherein R_3 and R_4 are as defined for formula I, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

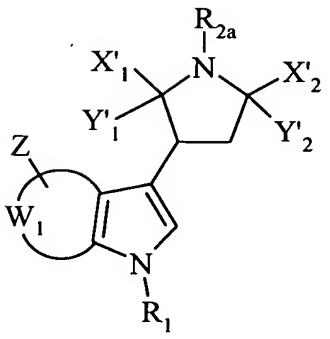
14- Compounds of formula (I) according to any one of claims 1 to 13, characterised in that R'_2 represents a hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, or a linear or branched $(C_1\text{-}C_6)$alkylene chain substituted by an NR_3R_4 group wherein R_3 and R_4 are as defined for formula I, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

15- Compounds of formula (I) according to claim 1 which are :

- 1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone,
- 2-methyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone,
- 2,5-dimethyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6(2*H*,5*H*,7*H*)-tetrone,
- 2-[2-(diethylamino)ethyl]-5-methyl-1*H*-dipyrrolo[3,4-a:3,4-c]carbazole-1,3,4,6-(2*H*,5*H*,7*H*)-tetrone,

their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

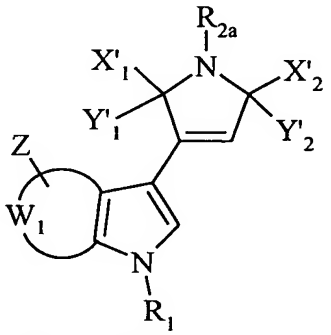
16- Process for the preparation of compounds of formula (I), according to claim 1, characterised in that there is used as starting material a compound of formula (II) :



(II)

wherein R_{2a} represents a hydrogen atom or a methyl group and R_1, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined for formula (I),

which is treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to yield a compound of formula (III) :

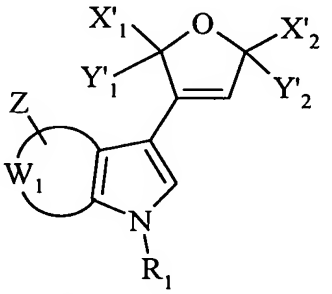


(III)

wherein R_1, R_{2a}, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

which compound of formula (III) is :

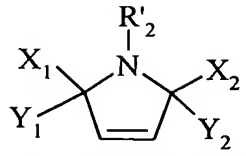
* *either* treated with aqueous sodium hydroxide solution and then placed in the presence of hydrochloric acid to yield a compound of formula (IV) :



(IV)

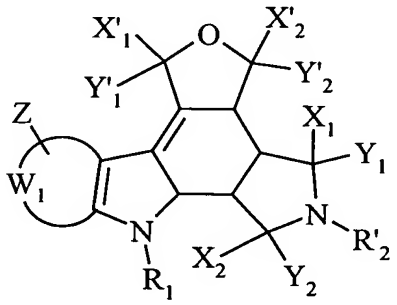
wherein R_1, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

which compound of formula (IV) is treated with a compound of formula (V) :

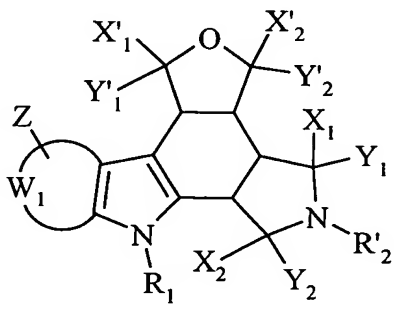


(V)

wherein R'_2, X_1, Y_1, X_2 and Y_2 are as defined for formula (I) to yield a compound of formula (I/a) and (I/b), a particular case of the compounds of formula (I) :



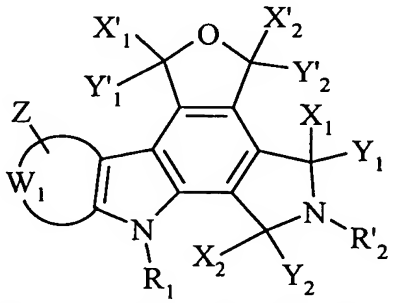
(I/a)



(I/b)

wherein R_1, R'_2, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

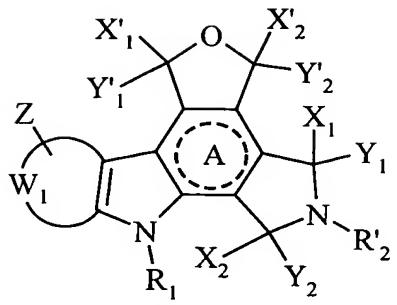
which compound(s) of formula (I/a) and/or (I/b) is(are) optionally subjected to the action of trifluoroacetic acid to yield a compound of formula (I/c), a particular case of the compounds of formula (I) :



(I/c)

wherein R_1, R'_2, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

the totality of the compounds of formulae (I/a), (I/b) and (I/c) constituting the compounds of formula (I/d) :



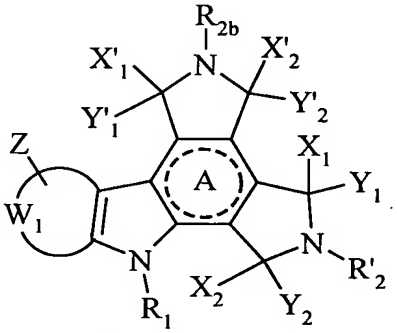
(I/d)

wherein A, R_1, R'_2, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

which compound of formula (I/d) is subjected to the action of a compound of formula (VII) :

$$R_{2b} - NH_2 \qquad (VII)$$

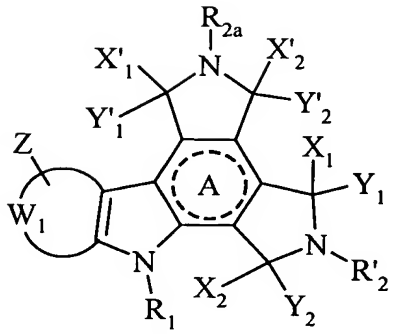
wherein R_{2b} has the same definition as R_2 in formula (I), with the exception of a hydrogen atom and a methyl group, to yield compounds of formula (I/e), a particular case of the compounds of formula (I) :



(I/e)

wherein A, R_1, R'_2, R_{2b}, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

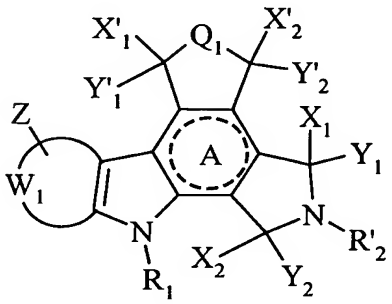
* *or* subjected in succession to the same reaction conditions as the compounds of formulae (IV), (I/a) and (I/b) to yield a compound of formula (I/f), a particular case of the compounds of formula (I) :



(I/f)

wherein A, R_1, R'_2, R_{2a}, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

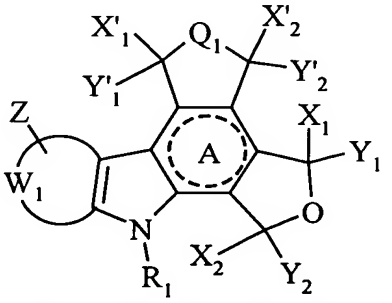
the totality of the compounds (I/d), (I/e) and (I/f) constituting the compounds of formula (I/g) :



(I/g)

wherein A, R_1, R'_2, Q_1, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

which compound of formula (I/g), when R'_2 represents a hydrogen atom or a methyl group, is optionally subjected in succession to the same reaction conditions as the compounds of formulae (III) to yield a compound of formula (I/i), a particular case of the compounds of formula (I) :



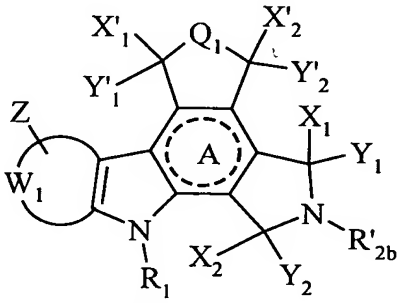
(I/i)

wherein A, R_1, Q_1, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

which compound of formula (I/i) is optionally subjected to the action of a compound (VIII) :

$$R'_{2b} - NH_2 \quad (VIII)$$

wherein R'_{2b} has the same definition as R'_2 in formula (I), with the exception of the definitions hydrogen atom and methyl group, to yield compounds of formula (I/j), a particular case of the compounds of formula (I) :



(I/j)

wherein A, R_1, R'_{2b}, Q_1, X_1, Y_1, X_2, Y_2, X'_1, Y'_1, X'_2, Y'_2, W_1 and Z are as defined hereinbefore,

the compounds of formulae (I/a) to (I/j) constituting the totality of the compounds of formula (I), which, if appropriate, are purified according to conventional purification techniques, may, if desired, be separated into their different isomers according to a conventional separation technique, the substituents R_a, R_b, R_c, R_d and R_e of which may be modified according to conventional methods of organic synthesis used in the field of sugar chemistry, and which compounds, if desired, are converted into addition salts with a pharmaceutically acceptable acid or base.

17- Pharmaceutical compositions comprising as active ingredient at least one compound of formula (I) according to any one of claims 1 to 15, on its own or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

18- Pharmaceutical compositions according to claim 17 for use as medicaments in the treatment of cancers.

received 04/11/02

INPI NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

PATENT OF INVENTION UTILITY CERTIFICATE

Intellectual Property Code - Book VI

PATENTS DIVISION
26 bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Tel.: 01 53 04 53 04 Fax: 01 42 93 59 30

DECLARATION OF INVENTORSHIP Page No. 1/3

(if the Applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink

Your references for this file *(optional)*		29285	
NATIONAL REGISTRATION NO.		0212847	
TITLE OF THE INVENTION (maximum 200 characters or spaces) New [3,4-a:3,4-c]carbazole compounds, a process for their preparation and pharmaceutical compositions containing them			
APPLICANT(S): LES LABORATOIRES SERVIER 12, place de La Défense 92415 COURBEVOIE Cedex FRANCE			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Name		PRUDHOMME	
Forenames		Michelle	
Address	Street	1, rue de Billom	
	Postal code and town	6300	CLERMONT-FERRAND
Belonging company *(optional)*			
Name		HUGON	
Forenames		Bernadette	
Address	Street	Espace Neyron 30, rue Villeneuve	
	Postal code and town	63000	CLERMANT-FERRAND
Belonging company *(optional)*			
Name		ANIZON	
Forenames		Fabrice	
Address	Street	2, chemin des vignes	
	Postal code and town	63720	ENNEZAT
Belonging company *(optional)*			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) 16 October 2002 (signature) Sabine WENGER, Patent Engineer			

received 04/11/02

INPI NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

PATENT OF INVENTION UTILITY CERTIFICATE

Intellectual Property Code - Book VI

PATENTS DIVISION
26 bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Tel.: 01 53 04 53 04 Fax: 01 42 93 59 30

DECLARATION OF INVENTORSHIP Page No. 2/3

(if the Applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink

Your references for this file *(optional)*		29285	
NATIONAL REGISTRATION NO.		0212847	
TITLE OF THE INVENTION (maximum 200 characters or spaces) New [3,4-a:3,4-c]carbazole compounds, a process for their preparation and pharmaceutical compositions containing them			
APPLICANT(S): LES LABORATOIRES SERVIER 12, place de La Défense 92415 COURBEVOIE Cedex FRANCE			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Name		HICKMAN	
Forenames		John	
Address	Street	136, rue de Tocqueville	
	Postal code and town	75017	PARIS
Belonging company *(optional)*			
Name		PIERRE	
Forenames		Alain	
Address	Street	9, chemin des Bois Janeaudes	
	Postal code and town	78580	LES ALLUETS LE ROI
Belonging company *(optional)*			
Name		GOLSTEYN	
Forenames		Roy	
Address	Street	100, rue de Pontoise	
	Postal code and town	78780	MAURECOURT
Belonging company *(optional)*			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) 16 October 2002 (signature) Sabine WENGER, Patent Engineer			

received 04/11/02

INPI NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

PATENT OF INVENTION UTILITY CERTIFICATE

Intellectual Property Code - Book VI

PATENTS DIVISION

26 bis, rue de Saint Pétersbourg
75800 Paris Cedex 08

Tel.: 01 53 04 53 04 Fax: 01 42 93 59 30

DECLARATION OF INVENTORSHIP Page No. 3/3

(if the Applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink

Your references for this file *(optional)*		29285	
NATIONAL REGISTRATION NO.		0212847	
TITLE OF THE INVENTION (maximum 200 characters or spaces) New [3,4-a:3,4-c]carbazole compounds, a process for their preparation and pharmaceutical compositions containing them			
APPLICANT(S): LES LABORATOIRES SERVIER 12, place de La Défense 92415 COURBEVOIE Cedex FRANCE			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Name		RENARD	
Forenames		Pierre	
Address	Street	3, avenue du parc	
	Postal code and town	78150	CHESNAY
Belonging company *(optional)*			
Name		PFEIFFER	
Forenames		Bruno	
Address	Street	47, rue Ernest Renan	
	Postal code and town	95320	SAINT LEU LA FORET
Belonging company *(optional)*			
Name			
Forenames			
Address	Street		
	Postal code and town		
Belonging company *(optional)*			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) 16 October 2002 (signature) Sabine WENGER, Patent Engineer			